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MCDERMOTT WILL & EMERY  
600 13TH STREET, N.W.  
WASHINGTON, DC 20005-3096

EXAMINER

MARVICH, MARIA

ART UNIT	PAPER NUMBER
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1636

14

DATE MAILED: 06/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/807,519

Applicant(s)

KEEGAN ET AL.

Examiner

Maria B Marvich, PhD

Art Unit

1636

-- Th MAILING DATE of this communication appears on th cover sheet with the correspond nc address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 25 March 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 6-28 is/are pending in the application.
- 4a) Of the above claim(s) 14-28 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3,7-11 and 13 is/are rejected.
- 7) ☒ Claim(s) 2,6 and 12 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 and 9.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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### **DETAILED ACTION**

This office action is in response to an amendment filed 3/25/03. Claims 1-3 and 6-28 are pending in this application.

#### ***Election/Restrictions***

Applicant's election with traverse of Group I in Paper No. 13 is acknowledged. The traversal is on the grounds that the inventions of Groups I-III do relate to a "single general inventive concept" under PCT Rule 13.1 as the special technical feature does make a contribution over the prior art. The technical feature is the insulin secretory sequence operable linked to a heterologous protein specifically, somatotropin. Applicant argues that the technical feature is not represented in the Cullen reference in which the 5' non-coding region of the rat pre-proinsulin II leader sequence is fused to the IL-2 coding sequence. The sequence of Cullen et al. contains six amino acids of the N-terminal portion of the pre-proinsulin signal while the insulin secretory sequence is 24 amino acids according to applicant. Furthermore, the six amino acids could not be considered as sufficiently constituting the secretory signal.

The argument is not found persuasive because while Cullen et al in view of O'Mahoney does not teach all the limitations the instant invention, a review of the art reveals that the technical feature does not make a contribution over the art. As described in detail below, the technical feature is not a contribution over Ernst et al (US 5,082,783) in view of Paulson et al (US 5,858,751) further in view of Eskridge et al. (Journal of Cell Biology).

The requirement is still deemed proper and is therefore made FINAL. Therefore, claims 1-3 and 6-13 will be examined.

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### *Drawings*

Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see previous office action, paper number 12 (with attached PTO 948).

### *Claim Objections*

Claims 3 and 7 are objected to because of the following informalities: In claim 3, following SEQ ID NO: 1 "an" should be written "and". In claim 7, heterologous is misspelled. Appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 8-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ernst et al. (US 5,082,783) in view of Paulson et al. (US 5,858,751) further in view of Eskridge et al. Journal of Cellular Biology, December 1986, Vol 103, No 6 pp 2263-2272.

Applicant claims an expression cassette and recombinant mammalian host cell comprised of an insulin secretory signal linked to a heterologous sequence encoding somatotropin and a method of producing somatotropin.

Ernst et al. teach enhanced secretion of heterologous proteins by the addition of heterologous secretion signal sequences in a vector (abstract). A DNA signal sequence is

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described in column 6, line 37-55 as a sequence that is required for secretion. A vector containing the signal sequence operably linked to the heterologous protein is introduced into a host such as a bacterial, mammalian, fungal and plant cells (column 6, line 66-column 7, line 6). Growth hormone, also known as somatotropin, is a preferred heterologous protein (column 9, line 5-19). In example 5, the heterologous protein operably linked to a signal sequence is transformed into a host cell, expressed and recovered (Example 5). Ernst et al teach that the signal sequence can be any signal sequence but do not teach specifically that this sequence is the insulin secretory signal.

Paulson et al teach fusion of their gene of interest, i.e.  $\alpha$ -2, 3-N Sialytransferase, to a pre-insulin secretory signal in order to generate a soluble, secreted form of their gene product of interest (column 31, line 35- column 32, line 22 and column 46, line 1-22).

Eskridge et al. identify sequence information within the insulin sequence that mediates the efficient translocation of a fused protein, chloramphenical acetyltransferase (page 2265 second paragraph). Therefore, Eskridge et al. demonstrate that the signal sequence of insulin encodes all the information necessary to translocate and secrete heterologous proteins (abstract).

One of ordinary skill would have been motivated to use the pre-insulin secretory signal sequence disclosed by Eskridge et al and Paulson et al. in the expression construct of Ernst et al. to express growth hormone, somatotropin, for the expected benefit of recombinant expression of somatotropin in which the protein can be secreted from and isolated from the host cell (Ernst et al. column 1, line 19-26). Pre-insulin secretory sequence fused to a heterologous protein leads to a soluble secreted protein (Paulson et al. column 31, line 50-52 and Eskridge et al. page 2265, second paragraph). One of ordinary skill in the art would have been motivated to combine the

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pre-insulin secretory signal with the somatotropin protein because somatotropin, like insulin, is a polypeptide hormone and one of ordinary skill in the art would have had an expectation of success in using one of the most characterized polypeptide hormone secretory signals (Eskridge et al) to secrete another polypeptide hormone (somatotropin). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Ernst et al. with the signal sequence of Paulson et al or Eskridge et al, which generates the secreted recombinant proteins specified by Ernst et al. (Ernst et al, column 6, line 50-55) given the success of Eskridge et al and Paulson et al in generation of secreted fusion proteins using the preinsulin secretory signal. Given the teachings of the cited art of Eskridge et al. that exemplifies the well known use of the insulin signal sequence to translocate heterologous proteins and the level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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The term "substantially" in claim 3 is a relative term that renders the claim indefinite.

The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "substantially" is a relative one not defined by the claim, no single set of conditions is recognized by the art as being "substantial" and because the specification does not provide a standard for ascertaining the requisite degree, the metes and bounds of this claim cannot be established.

Claim 7 recites a "regulatory element that enables pulsatile expression" which is a broad, undefined term for which no description in the specification is provided. Pulsatile is defined as

- (a.) Capable of being struck or beaten; played by beating or by percussion; as, a tambourine is a pulsatile musical instrument.
- (a.) Pulsating; throbbing, as a tumor.

It is unclear how a regulatory element performs this function.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of regulatory elements that enable pulsatile expression of the polypeptide of interest.

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The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus. In the instant case, applicants only disclose one regulatory element, Melatonin Response Element (MRE). Neither the specification nor art disclose whether this element enables pulsatile expression of the polypeptide of interest. Given the diversity of regulatory elements and the uncertainty of the activity of any regulatory element to regulate in a pulsatile manner, it must be considered that a regulatory element that enables pulsatile expression must be empirically determined. Furthermore, due to the lack of definition as to what is meant by a regulatory element that enables pulsatile expression, it is unclear how to identify a regulatory element belonging to a genus of such elements. In an unpredictable art, the disclosure of one example in one genus would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Claims 1, 3, 7-11 and 13 are rejected.

Claims 2, 6 and 12 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.



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***Conclusion***


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (703) 605-1207. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-3291.

Maria B Marvich, PhD  
Examiner  
Art Unit 1636

May 29, 2003

  
DAVID GUZO  
PRIMARY EXAMINER